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Research Article

Sulforaphane Improves Cognitive Dysfunction in the Brain: A Systematic Review and Meta-Analysis

Xiaowen Sun[1], Caihui Guo[2] and Yi Zhu[3]*

[1]Master of the College of Food Science and Nutritional Engineering, China Agricultural University, Beijing, China

[2]Doctor of the College of Food Science and Nutritional Engineering, China Agricultural University, Beijing, China

[3]Professor of the College of Food Science and Nutritional Engineering, China Agricultural University, Whose Research Interests are Nutrition and Food Safety, Beijing, China

***Corresponding Author:** Yi Zhu, Professor of the College of Food Science and Nutritional Engineering, China Agricultural University, Whose Research Interests are Nutrition and Food Safety, Beijing, China.

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Abstract

Sulforaphane is a sulfur-containing compound, also known as isothiocyanate, which widely exists in cruciferous plants. In addition to its potent antioxidant and anti-cancer properties, sulforaphane has been found in some studies to have a beneficial impact on cognitive function and to partially alleviate cognitive impairment. Therefore, this paper summarized the effects of sulforaphane on cognitive brain function in many contexts. Using a systematic review and meta-analysis. A total of 18 articles were included, Research objects included people and animals. The results showed that the improvement rate of sulforaphane intake on cognitive impairment was statistically significant in human (RR = 3.54, 95% CI = {0.57 - 6.50}, P = 0.02) and mouse experiments (RR = 5.43, 95% CI = {2.70 - 8.16}, P = 0.001). Thus, Sulforaphane can improve cognitive impairment.

Keywords: Sulforaphane; Cognitive Impairment; Improvement; Neurodegenerative Disease

Introduction

Cognitive refers to the process by which the human brain takes in information from the outside world and uses sophisticated processing to convert it into internal mental activities so that knowledge can be learned and applied (Chunshan Zhao, 2016) [1]. Normal cerebral cortex function is the foundation of cognition, and any factor that results in aberrant cerebral cortex anatomy and function might impair cognitive function. Abnormalities in learning, memorization, and thinking judgment are referred to as cognitive impairment (Ball H A., *et al*. 2020) [2]. According to the degree of cognitive impairment, it can be divided into mild cognitive impairment (MCI) and dementia. Diagnostic and Statistical Manual of Mental Disorders 5th edition, DSM-5 lists a range of causes of cognitive impairment, including Alzheimer's disease, cerebrovascular disease, brain tumors, frontotemporal lobe degeneration, human immunodeficiency virus infection, Huntington's disease, Louis body disease, Parkinson's disease, prion diseases, psychotropic drug use, and traumatic brain injury (Tucha O., *et al*. 2020; Leece R., *et al*. 2017; Brown P D., *et al*. 2006; Lin N U., *et al*. 2013 ; Douw L., *et al*. 2009) [3-7].

Sulforaphane (SFN), also known as [1-isothiocyanate-4-(methyl sulfinyl) butane], is an aliphatic isothiocyanate produced by the hydrolysis of its inactive precursor glucosinolates (glucoraphanin, GF) by myrosinase (VANDUCHOVA, ANZENBACHER, ANZENBACHEROVA 2019) (Its chemical structure is shown in Figure 1) [8]. This precursor chemical is present in all parts of cruciferous vegetables, such as Brussels sprouts, cauliflower, broccoli, and cabbage, but it is

most concentrated in the seeds (Schepici, Bramanti, Mazzon., *et al.*) [9]. The primary glucosinolate in broccoli, glucoraphanin, hydrolyzes to produce SFN. The biosynthesis of SFN occurs through hydrolysis, which involves myrosinase in plants, which, together with the inactive form of episulfide (ESP) proteins, leads to the formation of SFN. Sulforaphane has been proved to be safe and harmless and has been widely studied because of its various protective effects *in vivo* pathology and *in vitro* experimental model studies, such as antioxidant, anti-inflammatory and anticancer effects (Fahey and Talalay 1999; Mokhtari R B 2017; Kim and Park 2016) [10-12]. And There are positive effects on chronic inflammatory diseases and associated immune diseases (Liao Y., *et al*. 2023) [13]. Pharmacokinetic studies showed that the plasma concentration of SFN in human body increased rapidly, reaching a maximum of a few hours after oral administration of broccoli (Ghawi, Methven, Niranjan 2013; Hwang and Jeffery 2005) [14,15]. After being absorbed, SFN can easily cross the blood-brain barrier (BBB), suggesting that it may have potential activity in the central nervous system (CNS).

At present, it has been proven that SFN not only has the effects of anti-oxidation, anti-cancer, anti-inflammation and anti-apoptosis, but also can play a certain role in the treatment of neurological diseases and further play a role in brain cognitive function (Qianqian Li 2022; Zhang Y., *et al*. 2022; Zongxiang Li 2024) [16-18]. Many studies have shown that SFN is also related to the reversal of cognitive, learning and memory impairment induced by scopolamine, lipopolysaccharide and okadaic acid in rodents. In neurotoxicity models, SFN has been shown to inhibit neurotoxicity induced by a variety of toxic factors, such as hydrogen peroxide, prion proteins, hyperammonemia and methamphetamine (Schepici, Bramanti, and Mazzon 2020) [19].

However, no pertinent meta-analysis literature has been published to date suggesting that sulforaphane can alleviate cognitive impairment brought on by certain illnesses, including diabetes, lead exposure, brain injury, epilepsy, and so on. Sulforaphane's ability to improve cognitive impairment under normal circumstances was examined in this study, along with its ability to improve cognitive impairment brought on by a number of illnesses.

Method

Research registration

This research has been registration in the INPLASY, and the DOI is 10.37766/inplasy2024.10.0117.

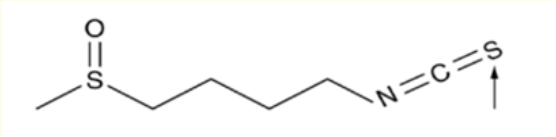

Figure 1: Chemical structure of SFN. The arrow indicates its bioactive group.

Literature retrieval and screening

This study was conducted according to the guidelines of the preferred report project (PRISMA) of systematic review and meta-analysis. PubMed, Web of Science, Google Academic, Zhiwang and Wanfang databases were selected as document retrieval databases, and the keywords "sulforaphane", "improvement", "cognitive impairment" and "neurodegenerative diseases" were used as search words.

Document retrieval was completed independently by two reviewers, reading the title and abstract of the article for preliminary screening, and the included articles come from any year, with no language restrictions, no age restrictions, and no gender restrictions. The subjects included human, animal and cell experiments, and the dose, duration and frequency of intervention were not limited. The control group was treated with placebo or no treatment. After the preliminary screening, the initial literature retrieval results were a total of 275 articles. 172 articles were excluded because they were reviews, the number of years of publication was unknown, and they had nothing to do with sulforaphane. After reviewing the content of the study and its relevance to the research design, as well as the integrity of the experimental results, 42 articles were excluded, and a total of 18 articles were retained for this study (The filtering process is shown in Figure 2).

Data extraction

Through the confirmation and discussion of the original paper, we eliminated the results that can not be used, and extracted the first author, publication year, research design, research objects, intervention characteristic types of subjects and experimental results. The included data was the average ± standard deviation model, and the result data that can not be used is transformed by software. At the same time, this paper studies multiple supporting groups in a study as individual data.

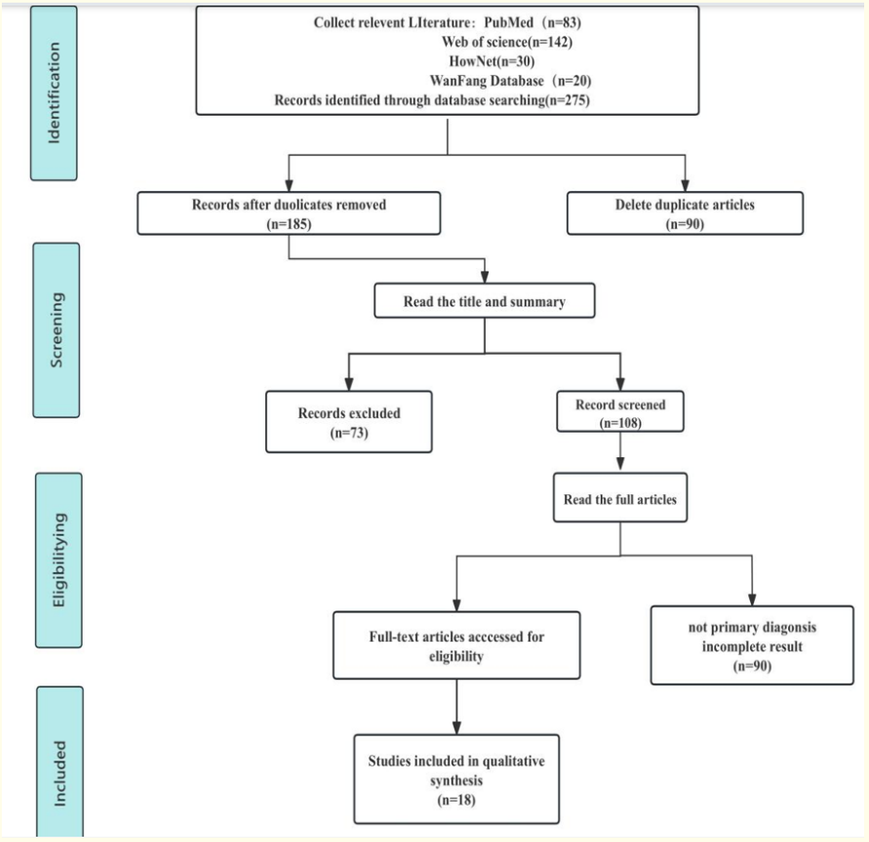

Figure 2: Flow chart of literature screening.

Bias risk assessment

Two reviewers used Cochrane to assess the bias risk of studies based on random sequence generation, assignment hiding, blindness of subjects and personnel, blindness of outcome assessment, incomplete outcome data, selective reporting, and so on. Then used Review manager to make a bias risk table.

Statistical analysis

The units of all evaluation indicators were standardized, and we used the average and standard deviation (SD) values of the markers to investigate the effect of the collected data. For the study with only standard error (SE), the square root of the sample size was used to convert SE into SD. For the data going in and out of the present variance and P value, Revman calculate was used for data conversion. The transformed data were analyzed by the review manager. The merged data were analyzed by a fixed effect model, and the data were expressed as the weighted average difference (WMD) and 95% confidence interval (Cl) of the continuous results.

Subgroup analysis was carried out according to the type of subjects. At the level of mesh meta-analysis, $P < 0.05$ indicates a statistically significant difference, and $P < 0.01$ indicates a statistically significant difference (Yang W., *et al.* 2020) [20]. The I^2 statistic test was used to estimate the percentage of heterogeneity between studies as the threshold: $I^2 < 50\%$, low heterogeneity; $50\% \leq I^2 \leq 5\%$, substantial heterogeneity; and $I^2 > 75\%$, high heterogeneity. In meta-analysis, when 95% CI is outside 95% CI of aggregate effect, it is defined as an outlier. It should be noted that, according to the literature recommendation, the meta-analysis generally recommends that at least 10 studies are included (Yang W., *et al.* 2023) [21]. The data were analyzed by random effect model. Based on the results of the initial analysis, we conducted a sensitivity analysis using the one-by-one elimination method to estimate the impact of omissions on each study. Funnel chart and Egger weighted regression test were used to evaluate the publication bias in order to explore the possibility of publication bias. When judging that it was statistically significant, the "pruning and filling" method [22] was used to adjust the effect.

Result

Overall bias risk assessment

We assessed the risk bias of the included use of sulforaphane in patients with cognitive impairment. As shown in figure 3 and figure 4, all experiments have a lower risk of bias.

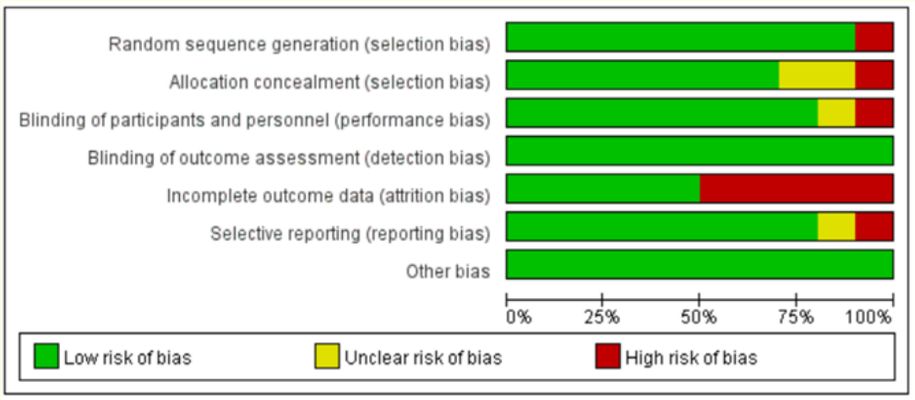

Figure 3: The judgment chart of the total risk percentage of each partial chair risk project The symbol in figure 3: red indicates high risk, yellow indicates ambiguity, and green indicates low and high risk.

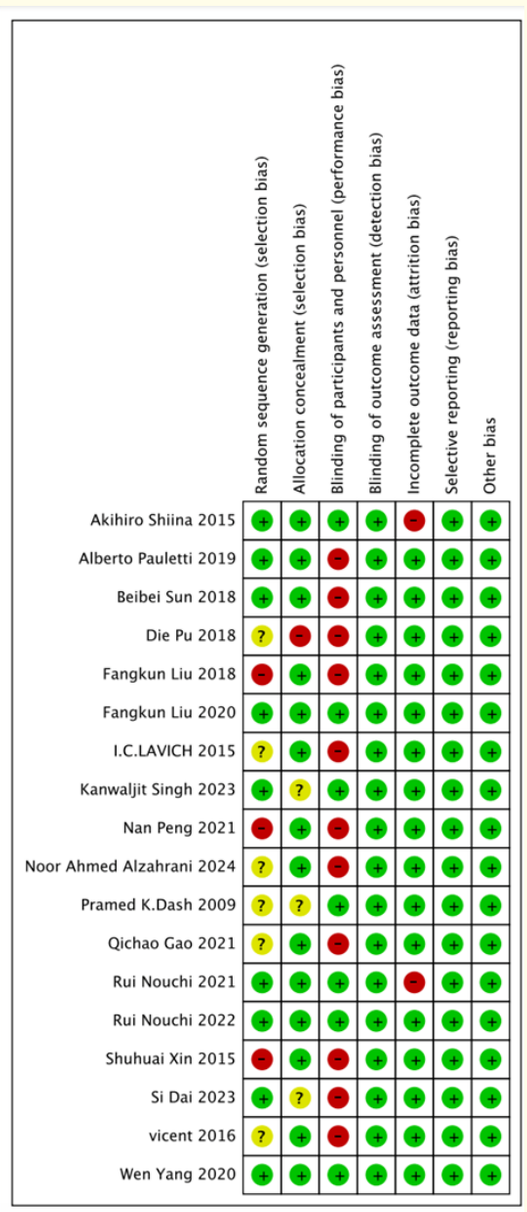

Figure 4: Judgment on the risk of partial chair in various studies Symbols:
Red indicates high risk, Yellow indicates unclear and Green indicates low risk.

Human experimental results

A total of 6 articles focusing on people were included in this study. The basic characteristics of each study are shown in Table 1, which involves patients' age, gender, sample size and experimental results. However, these studies Were slightly different in terms of intervention measures and evaluation indicators. The subjects included in the literature include patients with diabetes, Alzheimer's disease, brain injury and so on. The results showed that the improvement rate of cognitive impairment caused by sulforaphane intake was not statistically significant (RR = 3.54, 95% CI = {0.57 6.50}, P = 0.02) (The result are shown at Figure 5). Because of the high heterogeneity of $I^2 > 50\%$, the further subgroup analyses are needed. The results shown in the funnel chart are not completely symmetrical, suggesting that there may be a table bias (The result are shown at Figure 6).

Table 1: Table of basic information of human experiments included in literature.

1st Authers	Year	Number of experimental groups	Number of controls	Experimental conclusion
Si Dai	2023	26	14	Compared with the baseline, the total average score of sulforaphane group was significantly lower than that of placebo group (P < 0.05) (Dai S 2023) [23].
Akihiro Shiina	2015	6	3	Sulforaphane may be a supplement to improve the cognitive function of patients (Shiina A., *et al*. 2015) [24].
Ming Yang	2023	19	14	After treatment, the social cognition of the experimental group was significantly higher than that of the control group (Wald χ 2 = 4.825, p = 0.028) (Yang M 2023) [25].
Rui Nouchi	2022	72	72	12 weeks of sulforaphane intake increased the speed of processing, reduced overall negative emotions, and increased SEN-NAC levels (Nouchi R. 2022) [26]
Rui Nouchi	2021	36	36	Intake of SFN showed significant improvement in processing and working memory table, and could improve cognitive function (Nouchi R 2021) [27].
Fangkun Liu	2020	60	30	The memory impairment of patients was significantly improved after ingestion of sulforaphane for 8 weeks (Liu F., *et al*. 2020) [28]

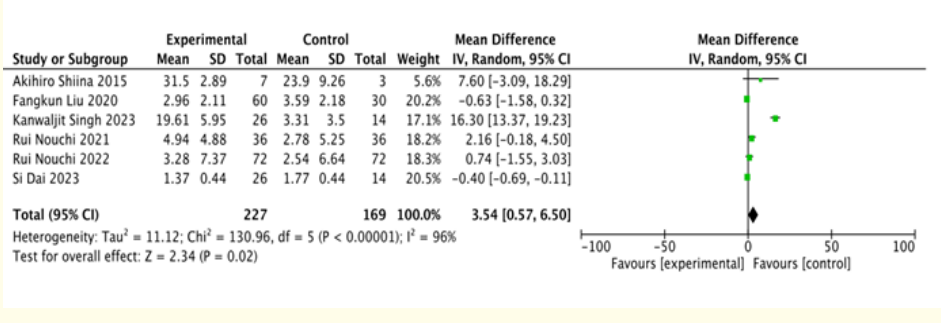

Figure 5: Forest map of sulforaphane improving cognitive impairment in human experiments.

RR = 3.54, 95% CI = {0.57~6.50}, $I^2 = 96\%$.

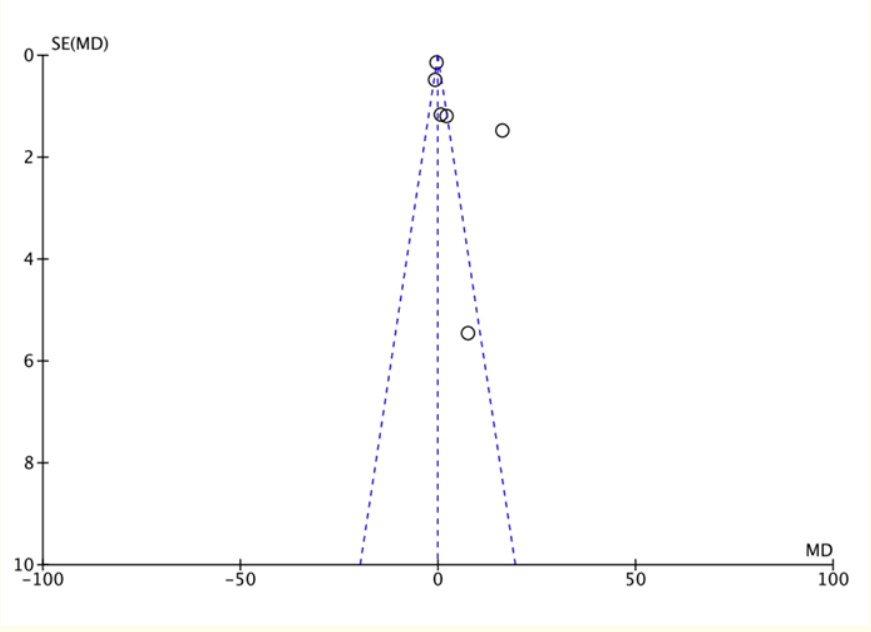

Figure 6: Funnel diagram of sulforaphane in improving human cognitive function.

Mouse experimental results

Rats and mice were the subject of 12 publications in all (Table 2 lists these publications in the literature). such as typical rats, mice with diabetes, mice with Alzheimer's disease, and mice exposed to lead. The findings demonstrated that sulforaphane improved cognitive function in these animal tests by 95%. The experimental results were statistically significant (CI = {1.86 - 7.59}, RR = 4.73, I^2 = 98%, P = 0.004), and the experimental group's average outcome index was lower than the control group's, suggesting that using sulforaphane to treat brain cognitive impairment is beneficial. Analysis of sensitivity is required. The results are not entirely symmetrical, as the funnel graphic indicates, which raises the possibility of publication bias.

Table 2: Basic information of animal experiments included in the literature.

1st Authers	Year	Number of experimental groups	Number of controls	Object of study	Experimental conclusion
I.C. LAVICH	2015	10	10	Iron-induced mice	SFN can reverse the decrease of fission protein DNM1L and synaptophysin in hippocampal mitochondria induced by iron, which leads to the recovery of iron-induced recognition memory impairment (Lavich I C., *et al*. 2015) [29].
Die Pu	2018	10	12	Diabetic mice	SFN treatment improved the cognitive impairment of diabetic mice (D. Pu 2018) [30]
Beibei Sun	2018	10	10	Lead exposed mice	SFN can reduce the increase of blood lead content caused by lead exposure in the early development stage of mice and reduce the accumulation of Aβ 1-40 and Aβ 1-42 in hippocampus and improve learning and memory ability (Sun B B., *et al*. 2018) [31].
Alberto Pauletti	2019	9	9	Epileptic mice	Sulforaphane treatment reduced oxidative stress in brain and blood and improved cognitive impairment in epileptic rats (Pauletti A., *et al*. 2019) [32].

Fangkun Liu	2018	60	30	Normal mice	After intake of sulforaphane for a period of time, the cognitive ability and memory function of mice were significantly improved (Liu F K., *et al*. 2018) [33].
Nan Peng	2021	10	10	Normal rat	SFN can improve the cognitive impairment caused by aging in rats (Peng N., *et al*. 2021) [34].
Noor Ahmed Alzahrani	2024	12	12	Lipopolysaccharide mice	SFN can prevent neurodegenerative diseases induced by lipopolysaccharide (Alzahrani N A., *et al*. 2024) [35].
Pramed K.Dash	2009	9	10	Brain injury mice	Sulforaphane can maintain brain function by protecting the blood-brain barrier, but the improvement of hippocampal dependent behavior was observed only when treatment with sulforaphane was started within an hour of injury (Dash P K., *et al*. 2009) [36].
Qichao Gao	2021	15	15	Diabetic mice	SFN can effectively enhance the cognitive behavior and improve the emotional abnormality of APP/PS1 mice. The possible mechanism is to reduce oxidative stress injury and enhance the synaptic plasticity of hippocampus. At the same time, it can increase the expression of synaptic related proteins SYP and PSD-95, and increase the number of dendrites and the density of dendritic spines in hippocampal CA1 region to improve structural plasticity (Gao Q C 2021) [37].
Shuhuai Xin	2015	10	10	Alzheimer's disease mice	SFN can significantly improve the cognitive function of AD model mice and protect neurons in hippocampal CA1 region (Xing S H 2014) [38].
vicent	2016	4	4	Hyperammonemia rats	Sulforaphane treatment promotes the differentiation of microglia from pro-inflammatory M1 phenotype to M2 phenotype and restores the spatial cognitive ability of rats with hyperammonemia. Sulforaphane therapy may help to improve mild cognitive impairment in patients with liver cirrhosis (Hernández-Rabaza V., *et al*. 2016) [39].
Wen Yang	2020	10	10	Normal mice	Sulforaphane therapy cognitive impairment and cognitive behavior improvement (Yang W., *et al*. 2020) [40].

Mice with diabetes, mice exposed to lead, and mice with iron-induced cognitive impairment were identified as the sources of the variations in the subground analysis. As can be seen in Figure 7 and Figure 8, the results were reanalyzed when these data were divided into two groups. The result is that RR = 1.67, 95% CI = {1.29 - 2.05}, $P < 0.0001$ and $I^2 = 0\%$. The differences between the groupings are minimal, and the experimental results are statistically significant. These variations might result from how sulforaphane affects certain illnesses that impair cognitive function. The results are not entirely symmetrical, as the funnel graphic indicates, which raises the possibility of publication bias.

Discussion

After meta-analysis of 18 articles, we can see that sulforaphane can improve brain cognitive impairment to a certain extent, but this advantage will be limited to the prevalence of the study subjects. For the high heterogeneity shown by human test results, it is possible to explain different methods of data collection or different evaluation indicators for each experiment, but 95% CI = {0.57-6.50} can still show that sulforaphane does have an improving effect. In the mouse experiment, the actual result was 95% CI = {1.29 ~ 2.05}. Due to the high heterogeneity, subgroup analysis was carried out. After subgroup analysis, according to Cohen's law, SMD ≤ 0.20 is a small level, 0.2 centilter SMD ≤ 0.5 is a medium level and SMD > 0.8 is a high level. That is, when the SMD value is greater than 0.8, the experimental results are reliable. In this study, the effect of sulforaphane intake on the improvement of brain cognitive function was assessed after sensitivity analysis, the sample size of the experimental group was 169, the sample size of the control group was 142, and the SMD value was 1.24, which was higher than 0.8. It is proved that the experimental results are reliable, and the intake of sulforaphane can improve cognitive function. Sulforaphane has a certain biological mechanism for the improvement of brain cognitive function. SFN has been proven to have beneficial effects on diseases such as AD (Alzheimer's Disease), Parkinson's

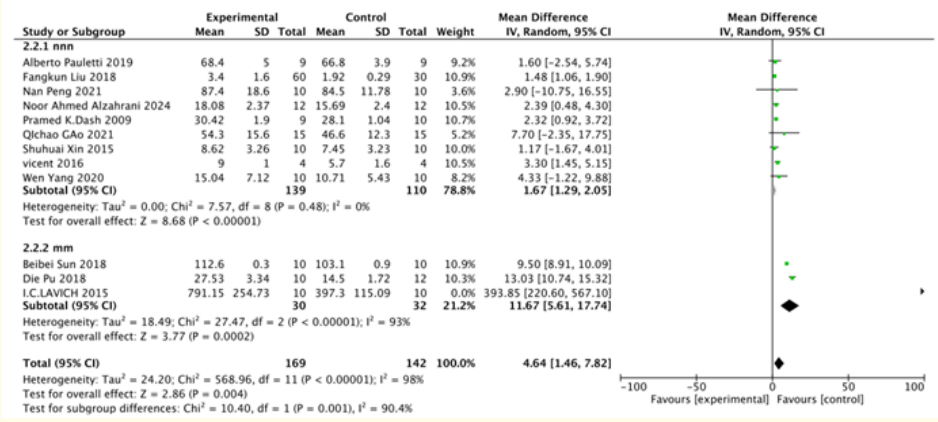

Figure 7: Forest map of the effect of sulforaphane on cognitive impairment in mouse experiment.

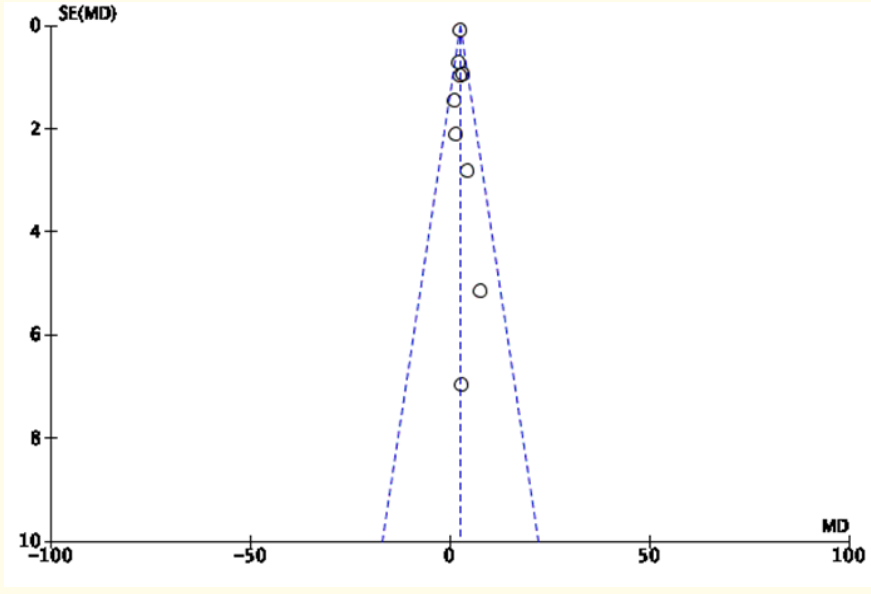

Figure 8: Funnel diagram for sensitivity analysis.

disease, and multiple sclerosis (Schepici, Bramanti, and Mazzon 2020) [41], serving as a potential therapeutic agent for neurodegenerative diseases. It is known that it can promote the growth and development of brain organs and neuronal differentiation (Copple IM 2012;Kim H V., *et al*. 2013; Tarozzi A., *et al*. 2010) [42-44], and the mechanism is related to the regulation of brain signal pathways and gene expression, so as to achieve the effect of treatment of depression (Andersen J K 2004;Leuner K 2012) [45,46]. Nrf2 plays an important role in the protective mechanism of many diseases, including cancer, neurodegenerative disease, cardiovascular disease, acute lung injury, chronic obstructive pulmonary disease, autoimmune disease and inflammatory disease. Korean scholars have found that SFN can activate the antioxidant response of Nrf2 to enhance emotional function and cognitive impairment (Zhang R., *et al*. 2015) [47]. Several animal studies (Jang and Cho 2016; Zhang and Talalay 1994; Pearson BL., *et al*. 2016) [48-50] have shown SFN to directly raise GSH levels by stimulating the Nrf2-Antioxidant Response Elements (ARE) and increasing the cellular antioxidant defense. SFN can also improve the anti-inflammatory effect, improve the negative symptoms and improve the working memory and cognitive level of schizophrenic patients by reducing the level of HsCRP, revealing a potential role for RS in treating anxiety disorders (Morroni F., *et al*. 2013) [51].

It is concluded that the reason for the high sensitivity may also be caused by the results of the experiment itself, in addition to the differences in evaluation indicators and data processing. For example, when cognitive impairment caused by brain injury was treated with sulforaphane, an improvement in hippocampal dependent behavior was observed only when sulforaphane treatment began within an hour of the injury. As for diabetic mice, it has been proven that sulforaphane can reduce blood sugar and improve diabetes, but it needs to be further proved whether it can improve the cognitive impairment caused by it.

The limitations of this study are as follows: 1. The included mouse age is not reported or marked, so it is easy to appear biased in meta analysis, which is not conducive to the accuracy and stability of the analysis. 2. Although strict literature retrieval has been carried out in the initial stage, there may still be omissions, and the number of literature experiments and inclusion of human subjects are relatively small.

Conclusion

The results of meta-analysis showed that sulforaphane intake can have a positive effect on brain cognitive function and improve brain cognitive impairment, but this improvement will be limited by drug administration and patients' own disease. The results showed that the intake of sulforaphane could effectively improve the cognitive impairment caused by lipopolysaccharide, transgene, Dongliang alkali induction, schizophrenia, depression, neuropathy and normal aging, but although the cognitive impairment caused by brain damage, diabetes and lead exposure also exists improving the effect will be poor due to some temporarily unclear reasons, so further experimental research is needed. It showed that sulforaphane is expected to be a dietary supplement, a special diet and other supplements or even alternative medical drugs to improve cognitive impairment.

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